

Evidence of genetic heterogeneity in congenital dyserythropoietic anaemia type I – response to Ahmed *et al*

We read with interest the correspondence article by Dr Ahmed and colleagues. The authors describe a consanguineous Kuwaiti family that included three siblings with congenital dyserythropoietic anaemia type I (CDA I). No homozygosity for the *CDAN1* gene was found, clearly suggesting that in this family, another CDA I gene may be involved. In our recent paper (Tamary *et al*, 2005), we described one CDA I patient in whom no mutations were found in the *CDAN1* gene. We concluded that the assumption that another gene may be involved 'cannot be formally dismissed'.

The present study of Ahmed *et al* provides the missing evidence for the presence of this other culprit gene in a subset of CDA I patients. The impairment of one component or another within a protein assembly or a signalling pathway may lead to the same phenotype as those currently assessed. It would be interesting to settle this issue unequivocally and to begin searching for a second gene.

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The association between *FANCD1/BRCA2* mutations and leukaemia

Patients with Fanconi Anaemia (FA) have an approximately 800-fold increased risk of leukaemia (Rosenberg *et al*, 2003). The rate of this complication was found to be higher in patients in the *FANCG* group when compared with *FANCA* and *FANCC*, and also to be higher in those with null compared with missense mutations in *FANCA* (Faivre *et al*, 2000). Further examination of genotype/leukaemia associations was recently provided by Barber *et al* (2005), who reviewed the rare group of FA patients with mutations in *FANCD1/BRCA2*, and stated that all of the cases of acute myeloid leukaemia (AML) occurred in patients with *BRCA2* mutations involving the splice site for IVS7.

Barber *et al* (2005) stated in the text that nine of 23 *FANCD1/BRCA2* patients developed AML, and that all of those cases had at least one allele with an IVS7 mutation. However, in their Table I they show five cases of AML among

six patients with a mutation in IVS7. In my review of 26 patients (23 from Barber's report and three additional literature cases; Howlett *et al*, 2002; Faivre *et al*, 2005; MacMillan *et al*, 2005), 10 cases with AML were identified, of whom only five had IVS7 mutations in one or both *BRCA2* alleles. In one case with no mutation information provided in the report, T-cell acute lymphocytic leukaemia (ALL) was followed by AML (MacMillan *et al*, 2005). There were three additional patients reported who had ALL, two T-cell and one B-cell (listed in Table I of Barber *et al*, 2005). Two of the five cases with AML and mutations in IVS7 were siblings, reducing the frequency of IVS7 mutations to four unrelated families among the nine families with cases of AML. One patient with a mutation in IVS7 had neutropenia at 5 months, a Wilms tumour at 9 months, underwent nephrectomy followed by stem cell transplant and died from a pulmonary haemorrhage

before 1 year of age without AML (MacMillan *et al*, 2005). Thus, five of six patients with mutations in IVS7 developed AML, while five of 20 without mutations in that region also had AML; the association of AML with IVS7 was still significant [OR 15, 95% confidence interval (CI) 1.1–750, $P = 0.02$, Fisher exact test] (STATA Statistical Software, Release 9; Stata Corporation, College Station, TX, USA), but the

correlation was neither as consistent nor as strong as stated by Barber *et al* (2005).

A time-dependent analysis sheds further light on this topic. The cumulative probability of AML or ALL combined reached a plateau of 79% by 10 years of age (Fig 1A); the probability of AML alone or after ALL was 60% by age 6 years (Fig 1B). The five patients with IVS7 mutations who developed AML all did so by age 3 years (median 2 years), while the four AML patients whose mutation was not in IVS7, for whom age information was available, developed AML by age 6 years (median also 2 years); the cumulative probability of AML was 41% in the latter group (Fig 1C). The cumulative incidence by age was significantly earlier in those with mutations in IVS7 ($P = 0.004$ by Cox regression).

The implication for patients with FA associated with mutations in IVS7 of *BRCA2* is that the risk of AML appears to be higher, and the age at onset younger, than among patients with other mutations in *BRCA2*. However, it must be emphasized that the risk of both AML and ALL is still very high in patients with mutations in other regions of *BRCA2*. Further studies of larger numbers of patients will be required to clarify and quantify the genotype/leukaemia associations among FA patients with mutations in *FANCD1/BRCA2*.

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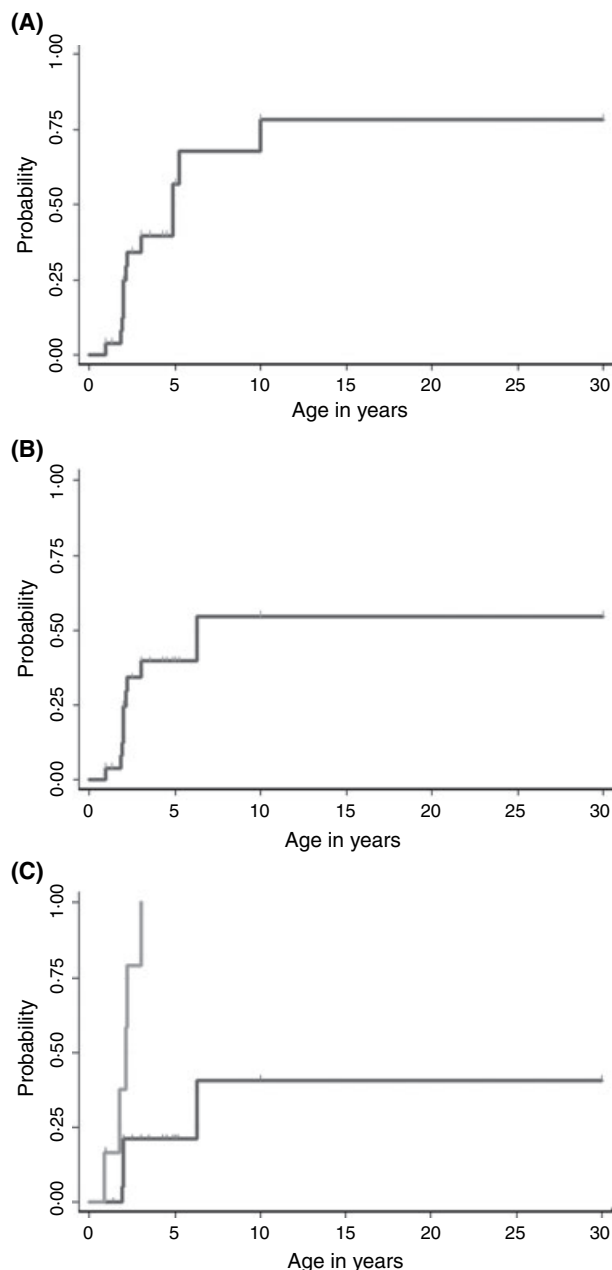


Fig 1. Leukaemia in patients with Fanconi anaemia because of mutations in *FANCD1/BRCA2*. (A) Probability of all types of leukaemia. (B) Probability of acute myeloid leukaemia (AML). (C) Probability of AML according to the presence or absence of a mutation in IVS7. Black line, mutations not in IVS7 ($n = 20$); grey line, mutations in IVS7 ($n = 6$).

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The association between *FANCD1/BRCA2* mutations and leukaemia – response to Alter

We are grateful to Dr Alter for confirming a statistically highly significant correlation of IVS7 splice site mutations and acute myeloid leukaemia in children with Fanconi's anaemia (FA) arising from bi-allelic *BRCA2* mutations by analysing details of 26 reported patients with bi-allelic *FANCD1/BRCA2* mutations. Albeit this correlation might not be as strong as we stated, we feel encouraged to have looked for IVS7 mutations in sporadic childhood leukaemia, where we did not find any. It should be emphasised that the important detailed statistical analysis on published data of the 26 patients by Dr Alter addresses the association between *FANCD1/BRCA2* mutations and leukaemia only in FA.

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Acute lymphoblastic leukaemia in Noonan syndrome

Noonan syndrome (NS), a congenital autosomal dominant disorder, presents with great variations in phenotypic expression. About 50% of patients have heterozygous mutations on chromosome 12q24 of the *PTPN11* gene.

In June 2004, a 17-year-old male with NS was referred to us because of severe thrombocytopenia (platelet count $19 \times 10^9/l$) and moderate anaemia (Hb 12.5 g/dl). At birth, the patient had shown facial dysmorphism (hypertelorism, low-set ears, high-arched palate), valvular pulmonic stenosis, cryptorchidism, pectus excavatum and short stature, which are all typical of NS (Tartaglia *et al*, 2001). Defects in factors VII, VIII and X had been documented since childhood. From 1997 onwards regular blood tests had shown moderate thrombocytopenia (range $65\text{--}135 \times 10^9/l$) and slight splenomegaly (mean diameter: 11.3 cm).

Clinical examination revealed an enlarged, painful spleen (22 cm), purpura and petechiae. A blood film showed 90% lymphoid blasts (white blood cell count, $4.46 \times 10^9/l$). Bone marrow biopsy and aspirate indicated acute lymphoblastic leukaemia (ALL) with a common B phenotype (CD34⁺, HLA-DR⁺, Tdt⁺, CD10⁺, CD19⁺, cCD22⁺, CD79 α ⁺). G-banded karyotype of bone marrow cells showed: 46 XY[8 cells]/41–45, XY[6 cells]/53 XXY, +4, +17, +18, +20, +21, +21[1 cell].

A hyperdiploid clone was suspected because one cell had a hyperdiploid karyotype and was demonstrated by fluorescence *in situ* hybridisation (FISH) with centromeric probes for chromosomes 13 of 21 (25% and 50% nuclei with five and six signals, respectively), 17 (60% and 10% nuclei with three and four signals, respectively), and 18 (40% nuclei with three signals). A PAC clone for the AML1/21q22 gene showed 26%